UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,661	01/31/2001	Paul S Hoffman	DALHO 1270-2	2441

7590 06/07/2004

STEPHEN E. REITER
FOLEY & LARDNER
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/647,661	HOFFMAN ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,13-25 and 28-44* is/are pending in the application.

4a) Of the above claim(s) *19-23 and 32-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,13-18,24,25,28-31 and 38-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/31/2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence alignments*.

DETAILED ACTION

1. The submission of the CRF and paper copy of the sequence listing is acknowledged. This application is now in compliance with 37 CFR 1.821-1.825.

2. Claims 1-6, 13-25, and 28-44 are pending.

Claims 19-23, and 32-37, drawn to non-elected inventions, are withdrawn from consideration.

Claims 1-6, 13-18, 24, 25, 28-31 and 38-44 are examined on the merits.

Claim Objections

3. Claim 15 is objected to because "Camphylobacter" appears to be a typographical error, and should read "Campylobacter".

Claim Rejections - 35 USC § 112

4. Claims 30, 31, and 38-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is indefinite because, whiled it provides for the use of a pharmaceutical formulation, the claim does not set forth any steps involved in the method/process. Therefore, it

is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 30 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 31 is indefinite because the phrase "said carrier" lacks antecedent basis in claim 24, from which claim 31 depends.

Claim 38 is indefinite because of the phrase "heterotypic cell". Claim 38 depends from claim 18, which does not contain any reference to a cell or organism. Therefore, it is not clear what is meant by "heterotypic cell" because there is no reference cell or organism to compare the cell to.

5. Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not set forth in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 17 is drawn to a conjugate wherein the nitroreductase is isolated from a particular bacterial strain, HP950. The specification fails to provide enough information for one of skill in the art to produce a bacterial strain with exactly the same characteristics as the HP950 H. pylori

strain. Even if the specification did provide enough information for one of skill in the art to produce an H. pylori strain with properties similar to those of the HP950 H. pylori strain, reproduction of an identical H. pylori strain is an unpredictable event. Because it does not appear that the HP950 H. pylori strain is publicly available or can be reproducibly isolated from nature without undue experimentation, one of ordinary skill in the art cannot be assured of the ability to practice the claimed inventions. Because claim 17 specifically requires the use of the HP950 H. pylori strain, a suitable deposit of the HP950 H. pylori strain is required, or evidence must be provided that the HP950 H. pylori strain well known and readily available to the public, or that it is reproducible without undue experimentation.

Furthermore, unless a deposit was made at or before the time of filing, a declaration filed under the 37 C.F.R. 1.132 is necessary to construct a chain of custody. The declaration, executed by a person in a position to know, should identify the deposited bacterial strain by its depository accession number, establish that the deposited bacterial strain is the same as that described in the specification, and establish that the deposited bacterial strain was in applicant's possession at the time of filing. Applicant is required to amend the specification to recite the accession number of the deposit, the date of deposit, a description of the deposited biological material, and the name and address of the depository. See In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

If the deposit is made under the provision of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the

provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the Budapest Treaty as the treaty leaves this specific matter to the discretion of each member state.

If the deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit, over his or her signature and registration number, averring:

(a) that all restrictions on the availability to the public of the material will be irrevocably removed upon the granting of a patent.

(b) that the material has been deposited under conditions that ensure that access to the material will be available during the pendancy of the patent application to one determined by the Commissioner to be entitled thereto under 35 CFR 1.14 and 35 USC 122.

(c) that the deposited material will be stored with all care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case at least thirty (30) years after the date of a deposit or for the enforceable life of the patent, whichever is longer.

(d) that the duty to replace the deposit should the depository be unable to furnish a sample when requested due to the condition of the deposit.

6. Claims 1-6, 13-16, 18, 24, 25, 28-31, and 38-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that each of the claimed inventions are broadly drawn to either a genus of compounds or to methods of using a genus of compounds, where the genus of compounds is not supported by an adequate description.

Claims 1-6, 13-16, 28 and 29 are drawn to conjugates comprising a nitroreductase that has a pI greater than about 6.0, 2 or more cysteine residues, and a preference for NADPH as an electron donor, and the nitroreductase is capable of converting metronidazole to one or more cytotoxic compounds, and to pharmaceutical compositions comprising the nitroreductase conjugate. Claims 18, 38-40, and 28 are drawn to nitroreductases that have a pI greater than about 6.0, 2 or more cysteine residues, and a preference for NADPH as an electron donor, and the nitroreductase is capable of converting metronidazole to one or more cytotoxic compounds, and to a pharmaceutical composition comprising the nitroreductase. Claims 24, 25, 30, 31, and 41-44 are drawn to methods comprising the administration of the claimed nitroreductase conjugates or nitroreductases.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is for purposes of the 'written description' inquiry, "*whatever is now claimed*" (see page 1117). The specification does not "clearly allow persons

of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nitroreductases that have a pI greater than about 6.0, 2 or more cysteine residues, and a preference for NADPH as an electron donor, and are capable of converting metronidazole or the conjugates comprising the reductases. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of manufacturing or testing to obtain the claimed compounds. In the instant case, the specification provides the amino acid sequence of metronidazole reductases encoded by polynucleotides isolated from 4 different strains of H. pylori that are sensitive to metronidazole. The amino acids sequences of each of the metronidazole reductases are almost identical. However, these 4 almost identical sequences are not representative of the genus of nitroreductases that are defined only by functional attributes, especially in view of the fact that the specification fails to correlate any structural features of the sequence with any of the functional limitations. These 4 almost identical sequences are not representative of the genus encompassing nitroreductases that are defined as having at least 90 percent sequence identity to the polypeptide encoded by the ORF of SEQ ID NO: 1. Without adequate description of the products the claimed methods of treatment requiring the use of the claimed products are not adequately described. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making or testing it. One cannot describe what one has not conceived. See Fides v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGFs were found unpatentable due to lack of written description for the broad class. Applicant is

reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112, is severable from its enablement provision. (See page 1115).

7. Claims 28, 30 and 41-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for selectively killing or inhibiting of the growth of target cells comprising the administration of a nitroreductase conjugated to an antibody that binds to target cells, does not reasonably provide enablement for methods of selectively killing or inhibiting the growth of target cells comprising the administration of a nitroreductase that is not conjugated to an antibody that binds to target cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 28 is drawn to a pharmaceutical formulation comprising a nitroreductase and a suitable carrier. Claims 30 is drawn to a therapeutic method for delivering to a patient a pharmaceutical formulation that comprises a nitroreductase. Claims 41-44 are drawn to methods for selectively killing or inhibiting the growth of target cells, comprising administering a nitroreductase in conjunction with metronidazole, wherein the nitroreductase converts the metronidazole into one or more toxic compounds. The target cells may be bacterial cells, viral cells, fungal cells, yeast cells, T-cells, B-cells, tissue cells, organ cells, diseased cells, tumor cells or neoplastic cells. The claimed methods lack a step that is directed to the preamble stated in the claimed that the methods are for "selectively killing or inhibiting the growth of target cells". Because the claimed inventions lack a step or recitation directed to how to practice the method so

that selective killing or growth inhibition is achieved, one of skill in the art would have to engage in undue experimentation to practice the full scope of the invention.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Antibody-enzyme conjugates were developed for the purpose of activating a prodrug at the specific site that the antibody targeted the enzyme as a way to decrease undesired side effects caused by systemic administration of chemotherapeutic agents (see Senter U.S. Patent 4,975,278; issue 12/04/1990, col. 1, lines 31-50). The use of a nitroreductase-antibody conjugate is known in the art for the purpose of activating the drug CB1954 to a cytotoxic form at the site of a tumor because the antibody is one that selectively binds to a tumor antigen (see Anlezark, U.S. Patent 5,633,158; issued 5/27/1997). However, the prior art does not teach the successful use of untargeted enzymes for the activation of a prodrug such as metronidazole. The inventions encompassed by the instant application read on systemic administration of an enzyme and a prodrug (metronidazole), which would cause the systemic conversion of metronidazole to toxic compounds. The specification contains no working examples demonstrating the feasibility of such a method where the enzyme is not targeted to a specific cell type.

Because the specification lacks working examples demonstrating how to use untargeted nitroreductase enzymes for the purpose of converting a prodrug such as metronidazole into a

toxic compound and further in view of the fact that prior art appears to teach away from the use of untargeted enzymes that convert prodrugs to toxic compounds, it would require undue experimentation to practice the full scope of the claimed inventions, which encompass the systemic administration of untargeted nitroreductases in conjunction with systemic administration of metronidazole.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 18, 28, 38, 39 and 40 are rejected under 35 U.S.C. 102(e) as being anticipated by either Kleanthous (U.S. P.G. Pub 2003/0158396; published 08/21/2003; effective filing date 07/29/1997) or Smith et al (U.S. P.G. Pub. 2004/0052799; published 03/18/2004; effective filing date 12/17/2997).

Claims 18 and 38-40 are drawn to nitroreductases that have a pI greater than about 6.o, 2 or more cysteine residues and a preference for NADPH as an electron donor and are capable of converting metronidozale to one or more cytotoxic compounds. The nitroreductase may be expressed in a heterotypic cell, such as bacterium, virus, retro-virus, yeast or a eukaryotic cell; and the expression vector used for the expression may have nucleic acid having freater than

about 90% homology to the ORF in SEQ ID NO: 1. Claim 28 is drawn to a pharmaceutical formulation comprising a nitroreductase of claim 18, where the recitation of pharmaceutical formulation is interpreted to be a recitation of intended use that does not structurally modify the nitroreductase.

Kleanthous teaches SEQ ID NO: 180 which is a protein with 210 amino acids and is encoded by a nucleic acid that has greater than 90 percent similarity in sequence to that of SEQ ID NO: 1 (see alignment). Kleanthous also teaches pharmaceutical formulations (page 13, para 77). Thus, Kleanthous teaches polypeptides that are the same as that claimed.

Smith teaches SEQ ID NO: 6487 which is a protein of 210 amino acids and is encoded by a nucleic acid that has greater than 90 percent similarity in sequence to that of SEQ ID NO: 1 (see alignment). Smith also teaches pharmaceutical formulations (page 79, para 176). Thus, Smith teaches polypeptides that are the same as that claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Anne L. Holleran
Patent Examiner
May 31, 2004